526 Rec'd PCT/PTO 23 JUN 2000

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	US APPLICATION NO (If known, see 37 CFR 1.5)
P65678US0	09/582328

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/08424	23 DECEMBER 1998	23 DECEMBER 1997

TITLE OF INVENTION

SERINE PROTEINASE INHIBITORS

APPLICANT(S) FOR DO/EO/US

FORSSMANN, Wolf-Georg; MAGERT, Hans-Jurgen; STANDKER, Ludger; KREUTZMANN, Peter

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ■ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ■ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ■ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ■ Other items or information:

    International Search Report
    PCT/IB/304 Form
    PCT/IB/308 Form
    First Page of Publication
    International Preliminary Examination Report

US APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/582328	PCT/EP98/08424	P65678US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) . . $670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . $760.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$970.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$840.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☒ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**20** - 20 =	-0-	x $18.00	$	
Independent Claims	**1** - 3 =	-0-	x $78.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 970.00	
Reduction by 1/2 for filing by **small entity**, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 970.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 970.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$	
TOTAL FEES ENCLOSED =				$ 970.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 970.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ --- to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:
Jacobson, Price, Holman & Stern, PLLC
400 7th Street, N.W., Suite 600
Washington, DC 20004
202-638-6666
CUSTOMER NUMBER: 00136

By William E. Player
William E. Player
Reg. No. 31,409

JPH&S 3/95

Atty. Dkt. No. P65678US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: FORSSMANN, et al.

App. No.: National Stage of PCT/EP98/08424

Filed: 23 December 1998

For: SERINE PROTEASE INHIBITORS

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to calculating the filing fee, please amend the captioned application as follows.

IN THE CLAIMS

Cancel claims 1-20 without prejudice or disclaimer.

Add the following claims.

21. A serine protease inhibitor, characterized by having a domain with four cysteines, and a sequence of 13 amino acids is present between the first and second cysteines, a sequence of 18 amino acids is present between the second and third cysteines, and a sequence of 2 amino acids is present between the third and fourth cysteines.

22. The serine protease inhibitor according to claim 21, characterized in that the sequence of the domain between the first and second cysteines is selected from

HEFQAFMKNGKLF,	SEYRKSRKNGRLF,
DDFKKGERDGDFI,	SEFRDQVRNGTLI,
SAFRPFVRNGRLG,	SEYRHYVRNGRLP,

KEYEKQVRNGRLF, DEFRRLLQNGKLF,

SQYQNQAKNGILF, AEYREQMKNGRLS, or

NEYRKLVRNGKLA, DEFRSQMKNGKLI.

23. The serine protease inhibitor according to claim 21, characterized in that the sequence between the second and third cysteines is selected from

PQDKKFFQSLDGIMFINK, TRENDPIQGPDGKMHGNT,

TRENDPVLGPDGKTHGNK, TREHNPVRGPDGKMHGNK,

TRESDPVRGPDGRMHGNK, TRENDPIEGLDGKIHGNT,

TRENDPIRGPDGKMHGNL, TRENDPVRGPDGKTHGNK,

TRENDPIQGPDGKVHGNT, TRESDPVRDADGKSYNNQ, or

TRESDPVRGPDGKTHGNK.

24. The serine protease inhibitor according to claim 21, characterized in that the sequence between the third and fourth cysteines of the domain is selected from AT, AL, AM, SM, or TM.

25. The serine protease inhibitor according to claim 21, having one of the following formulas:

- R_1-C-HEFQAFMKNGKLF-C-PQDKKFFQSLDGIMFINK-C-AT-C-R_2
- R_1-C-DDFKKGERDGDFI-C-PDYYEAVCGTDGKTYDNR-C-AL-C-R_2
- R_1-C-SAFRPFVRNGRLG-C-TRENDPVLGPDGKTHGNK-C-AM-C-R_2
- R_1-C-KEYEKQVRNGRLF-C-TRESDPVRGPDGRMHGNK-C-AL-C-R_2
- R_1-C-SQYQNQAKNGILF-C-TRENDPIRGPDGKMHGNL-C-SM-C-R_2
- R_1-C-NEYRKLVRNGKLA-C-TRENDPIQGPDGKVHGNT-C-SM-C-R_2

- R_1-C-SEYRKSRKNGRLF-C-TRENDPIQGPDGKMHGNT-C-SM-C-R_2
- R_1-C-SEFRDQVRNGTLI-C-TREHNPVRGPDGKMHGNK-C-AM-C-R_2
- R_1-C-SEYRHYVRNGRLP-C-TRENDPIEGLDGKIHGNT-C-SM-C-R_2
- R_1-C-DEFRRLLQNGKLF-C-TRENDPVRGPDGKTHGNK-C-AM-C-R_2
- R_1-C-AEYREQMKNGRLS-C-TRESDPVRDADGKSYNNQ-C-TM-C-R_2
- R_1-C-DEFRSQMKNGKLI-C-TRESDPVRGPDGKTHGNK-C-TM-C-R_2,

wherein R_1 is NH_2, an amino acid, or a peptide with up to 1000 amino acids, and R_2 is COOH, $CONH_2$, an amino acid, or a peptide with up to 1000 amino acids.

26. The serine protease inhibitor according to claim 21, characterized by containing

- a disulfide bridge between the first and fourth cysteines and/or between the second and third cysteines; or
- a disulfide bridge between the first and a fifth cysteine and/or between the second and fourth cysteines and/or between the third and a sixth cysteine.

27. The serine protease inhibitor according to claim 21, characterized by being a fragment of VAKTI-1 (SEQ. ID. NO. 1) or VAKTI-2 (SEQ. ID. NO. 2).

28. The serine protease inhibitor according to claim 27, characterized by being HF 6479 (SEQ. ID. NO. 3) or HF 7665 (SEQ. ID. NO. 4).

29. A nucleic acid coding for a serine protease inhibitor according to claim 21.

30. A medicament containing

- the serine protease inhibitor according to claim 21,
- a nucleic acid coding for the serine protease inhibitor, or

- the serine protease inhibitor and the nucleic acid coding for the serine protease inhibitor,

together with pharmaceutical vehicles.

31. The medicament according to claim 30, containing from 0.01 to 1000 mg per kg of body weight of the serine protease inhibitor.

32. Method of using the medicament according to claim 30, wherein the medicament is the serine protease inhibitor, for the treatment of acute or chronic cervix inflammations, inflammations of Bartholin's glands and other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleeding due to hyperfibrinolysis, and for the prophylaxis of lung emphysema formation in deficiencies of α_1-proteinase inhibitor.

33. Method of using the medicament according to claim 30, wherein the medicament is the nucleic acid coding for the serine protease inhibitor, in gene therapy for the treatment and prophylaxis of acute or chronic cervix inflammations, inflammations of Bartholin's glands and other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleeding due to hyperfibrinolysis, and lung emphysema formation in deficiencies of α_1-proteinase inhibitor.

34. Antibodies or antibody fragments against epitopes of the serine protease inhibitor according to claim 21.

35. Poly- or oligonucleotides which will hybridize to regions of the cDNA or corresponding RNA under stringent conditions and optionally prevent the expression of coding regions of the genes coding for the serine protease inhibitor according to claim 21.

36. A diagnostic agent containing at least one of the antibodies or antibody fragments according to claim 34.

37. A medicament containing the antibodies or antibody fragments according to claim 34 in therapeutically effective amounts.

38. Method of using the medicament according to claim 37 for the treatment of diseases involving too high an expression of a serine protease inhibitor, characterized by the antibodies or antibody fragments having a domain with four cysteines, and a sequence of 13 amino acids is present between the first and second cysteines, a sequence of 18 amino acids is present between the second and third cysteines, and a sequence of 2 amino acids is present between the third and fourth cysteines.

39. DNA coding for the serine protease inhibitor according to claim 21.

40. The DNA according to claim 39 having the SEQ. ID. NO. 5 or SEQ. ID. NO. 6.

REMARKS

Claims 21-40 are presented for consideration..

Claims 21-40 correspond to canceled claims 1-20, respectively, revised to eliminate multiple dependencies and to, otherwise, more clearly define the instant invention.

Favorable action is requested.

Respectfully submitted,

William E. Player
Reg. No. 321,409
JACOBSON, PRICE, HOLMAN & STERN, PLLC

JACOBSON, PRICE, HOLMAN & STERN, PLLC
400 Seventh Street, N.W.
Washington, D.C. 20004
Tel. No.: 202-638-6666
Atty. Dkt. No. P65678US0
WEP/id

R:\HOME\emennillo\June\P65678-PRE

SMB

Serine Protease Inhibitors

The present invention relates to serine protease inhibitors, cDNA coding for serine protease inhibitors, medicaments containing such inhibitors or their coding nucleic acid, use of the compounds according to the invention for the preparation of medicaments for the treatment of various indications, antibodies or antibody fragments against epitopes of the compounds according to the invention, poly- or oligonucleotides which will hybridize to genes of the compounds according to the invention, a diagnostic agent for detecting the compounds according to the invention, and medicaments containing antibodies or poly- or oligonucleotides according to the invention.

Proteolytic processes play an important physiological role in all organisms; a distinction has to be made between non-specific and specific proteolytic reactions. The former include, for example, the digestion of food in the digestive tract by endopeptidases, and the intracellular degradation of used endogenous substances and phagocytosed materials by lysosomal proteases. Specific proteolyses mostly serve for the conversion of a proenzyme to its active form, as in the conversion of trypsinogen to trypsin, and of chymotrypsinogen to chymotrypsin, and in the callicrein-kinin cascades and the blood clotting cascade. Depending on the structure of the reactive site of the proteinases involved, they are classified into the classes of serine proteases (e.g., chymotrypsin, trypsin, elastase and cathepsin G), aspartate proteases (e.g., cathepsin D, cathepsin E and pepsin), cysteine proteases (e.g., cathepsin B, cathepsin H and cathepsin L), and the metallo-proteases (e.g., collagenase and thermolysin).

In order to be able to correct the proteolytic processes which often proceed in a cascade, the organisms is provided with a number of other proteins, the protease inhibitors (for a survey, see Laskowski and Kato, 1980, and Bode and Huber, 1992). Thus, the liver-synthesized human plasma protease inhibitors α_1-

antichymotrypsin and α_1-proteinase inhibitors protect the lung tissue from non-specific attack by the proteinases cathepsin G and elastase from polymorphonuclear lymphocytes. When the balance between proteases and their specific inhibitors is disturbed, pathological effects may arise. For example, an excess ratio of elastase to α_1-proteinase inhibitor increases the risk of formation of a lung emphysema by a factor of about 20 to 30 in patients with a genetically caused deficiency in this factor as compared to the normal population (Carrel and Owen, 1980). With smokers, the formation of an emphysema is promoted by oxidation of the amino acid methionine which is present in the reactive site of the α_1-proteinase inhibitor by oxidants contained in cigarette smoke (Miller and Kuschner, 1969; Ohlsson et al., 1980). Also in the case of infection with Gram-negative bacteria, their endotoxins can cause disintegration of phagocytes and thus the secretion of lysosomal proteases, which may cause an uncontrolled damage to tissues and inflammations due to the increased consumption of protease inhibitors. For this reason, certain protease inhibitors have a high therapeutic potential (see, e.g., Fritz, 1980).

It has been the object of the present invention to provide further inhibitors of serine proteases. In addition, the genes or cDNA coding for the inhibitors according to the invention should be provided.

A specific feature of the serine protease inhibitors according to the invention is that the serine protease inhibitor has a domain with four cysteines, and a sequence of 0 to 20 amino acids is present between the first and second cysteines, or the serine protease inhibitor has a domain with six cysteines, and a sequence of 7 to 20 amino acids is present between the first and second cysteines.

Preferably, a sequence of 13 amino acids is present between a first and a second cysteine, and/or a sequence of 18 amino acids is present between a second and a third cysteine, and/or a sequence of 2 amino acids is present between a third and a fourth cysteine.

It is particularly preferred that the sequence between a first and a second cysteine be selected from

HEFQAFMKNGKLF,
DDFKKGERDGDFI,
SAFRPFVRNGRLG,
KEYEKQVRNGRLF,
SQYQNQAKNGILF,
NEYRKLVRNGKLA,
SEYRKSRKNGRLF,
SEFRDQVRNGTLI,
SEYRHYVRNGRLP,
DEFRRLLQNGKLF,
AEYREQMKNGRLS, or
DEFRSQMKNGKLI

and/or the sequence between a second and a third cysteine be selected from

PQDKKFFQSLDGIMFINK,
TRENDPVLGPDGKTHGNK,
TRESDPVRGPDGRMHGNK,
TRENDPIRGPDGKMHGNL,
TRENDPIQGPDGKVHGNT,
TRENDPIQGPDGKMHGNT,
TREHNPVRGPDGKMHGNK,
TRENDPIEGLDGKIHGNT,
TRENDPVRGPDGKTHGNK,
TRESDPVRDADGKSYNNQ, or
TRESDPVRGPDGKTHGNK

and/or the sequence between a third and a fourth cysteine be selected from

AT, AL, AM, SM, or TM.

It is particularly preferred that the serine protease inhibitor according to the invention correspond to one of the following formulas:

R_1-C-HEFQAFMKNGKLF-C-PQDKKFFQSLDGIMFINK-C-AT-C-R_2
R_1-C-DDFKKGERDGDFI-C-PDYYEAVCGTDGKTYDNR-C-AL-C-R_2
R_1-C-SAFRPFVRNGRLG-C-TRENDPVLGPDGKTHGNK-C-AM-C-R_2
R_1-C-KEYEKQVRNGRLF-C-TRESDPVRGPDGRMHGNK-C-AL-C-R_2
R_1-C-SQYQNQAKNGILF-C-TRENDPIRGPDGKMHGNL-C-SM-C-R_2
R_1-C-NEYRKLVRNGKLA-C-TRENDPIQGPDGKVHGNT-C-SM-C-R_2
R_1-C-SEYRKSRKNGRLF-C-TRENDPIQGPDGKMHGNT-C-SM-C-R_2
R_1-C-SEFRDQVRNGTLI-C-TREHNPVRGPDGKMHGNK-C-AM-C-R_2
R_1-C-SEYRHYVRNGRLP-C-TRENDPIEGLDGKIHGNT-C-SM-C-R_2
R_1-C-DEFRRLLQNGKLF-C-TRENDPVRGPDGKTHGNK-C-AM-C-R_2
R_1-C-AEYREQMKNGRLS-C-TRESDPVRDADGKSYNNQ-C-TM-C-R_2

R_1-C-DEFRSQMKNGKLI-C-TRESDPVRGPDGKTHGNK-C-TM-C-R_2,

wherein R_1 is NH_2, an amino acid, or a peptide with up to 100 amino acids, and R_2 is COOH, $CONH_2$, an amino acid, or a peptide with up to 100 amino acids.

It is further preferred that the serine protease inhibitor contains one or more disulfide bridges. It is particularly for it to contain a disulfide bridge between the first and fourth cysteines and/or between the second and third cysteines, or to contain a disulfide bridge between the first and fifth cysteines and/or between the second and fourth cysteines and/or between the third and sixth cysteines.

Preferred representatives of the serine protease inhibitors according to the invention are the compounds HF 6479 and HF 7665, and fragments of proteins VAKTI-1 and VAKTI-2 according to Figures 1 and 2.

In addition to the amino acid sequence of the preferred compounds according to the invention, further information about the cDNA coding for the compounds according to the invention can also be seen from Figures 1 to 3. In particular, the corresponding motives and primer-hybridizing sites are indicated.

Compound HF 3479 according to the invention has a mass of 6,479 Dalton, and that of HF 7665 is 7,665 Dalton; both have been purified from hemofiltrate.

According to the invention, a cDNA coding for the compounds according to the invention, especially a cDNA having the nucleic acid sequence according to Figures 1 to 2, is also claimed.

The compounds according to the invention are useful as medicaments. In this case, they are administered together with pharmaceutically acceptable vehicles.

The medicaments according to the invention containing the protease inhibitors according to the invention are preferably administered in amounts of from 1 to 100 mg/kg of the patient's body weight. As the dosage form, all galenic formulations for peptide active substances may be used. The medicaments containing nucleic

acids according to the invention are preferably administered in amounts of from 0.1 to 100 mg/kg of body weight of a corresponding patient. In this case, the galenic dosage forms which may be used are those which are suitable for the administration of nucleic acids without rendering the nucleic acids ineffective by metabolic influences before they have reached their site of action. For example, liposomes in which the nucleic acids are contained can be employed as a galenic dosage form.

The compounds according to the invention can be used, in particular, for the treatment of acute or chronic cervix inflammations, inflammations of Bartholin's gland or other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleedings due to hyperfibrinolysis, and for the prophylaxis of lung emphysema formation in deficiencies of α_1-proteinase inhibitor.

The compounds according to the invention can be administered in deficiencies of serine protease inhibitors to correct endogenous defects. The nucleic acids may also be used in gene therapy, either directly or coupled to suitable vehicles. Suitable vectors include, in particular, attenuated adenoviruses into which the corresponding genes have been incorporated.

The polypeptides according to the invention, especially VAKTI-I and VAKTI-II, can serve for the preparation of antibodies or antibody fragments. These are simply prepared by the immunization of appropriate mammals. By per se known operations, the antibodies may also be humanized so that such antibodies can also be employed for therapeutic use. Antibodies or antibody fragments can then by employed for the regulation of diseases in which the protease inhibitors are expressed in a pathological way. Also, antisense nucleic acids complementary to the nucleic acids according to the invention may also be employed in therapeutical use in overexpressions of the protease inhibitor genes.

The compounds according to the invention can be easily prepared by per se known methods of peptide or nucleotide synthesis. Preparation of the compounds by genetic engineering is also possible.

Those skilled in the art will recognize that fragments of the polypeptides according to the invention may also be used provided that they retain the inhibitory properties of the serine protease inhibitors. Those skilled in the art know how to find such fragments. Thus, this may be accomplished, for example, by a selected enzymatic cleavage of the compounds according to the invention. Side-chain modified amino acids may also be employed. N- or C-terminally modified polypeptides may also be used. In particular, phosphorylated, glycosylated, methylated, acetylated or similarly modified polypeptides can be employed provided that they do not substantially affect the activity of the serine protease inhibitors.

Derivatives of the nucleic acids according to the invention which have modified triplet structures in accordance with codon usage may also be used. In addition, nucleic acids according to the invention also include those which are more stable towards degradation by nucleases as compared with the native compounds, for example, the corresponding SODN derivatives usually employed in antisense technology to give the antisense structures a more stable design towards enzymatic attack.

Structures homologous to the polypeptides may also be used. In particular, these include polypeptide structures in which amino acids have been exchanged. Thus, for example, conservative amino acid substitutions in highly conserved regions can be considered as follows: any isoleucine, valine and leucine amino acid can be exchanged for any other of these amino acids, aspartate can be exchanged for glutamate and vice versa, glutamine for asparagine and vice versa, serine for threonine and vice versa. Conservative amino acid substitutions in less highly conserved regions can be as follows: Any of the amino acids isoleucine, valine and leucine for any other of these amino acids, aspartate for glutamate and vice versa, glutamine for asparagine and vice versa, serine for threonine and vice versa, glycine for alanine and vice versa, alanine for valine and vice versa, any of the amino acids leucine, isoleucine or valine for methionine, lysine for arginine and

vice versa, either of the amino acids arginine or lysine for either of the amino acids aspartate or glutamate, either of the amino acids arginine or lysine for histidine, glutamine for glutamate and vice versa, and asparagine for aspartate and vice versa.

The mode of action of the peptides according to the invention will be illustrated by the following Example.

Example

Measurement of protease inhibition by HF 7665

Measuring composition:

84 µl	measuring buffer (0.1 M HEPES, pH 7.5; 0.5 M NaCl)
1 µl	trypsin (1 mg/ml in 1 mM HCl, 20 mM $CaCl_2$)
5 µl	L-BABNA (6 mg/ml N-α-benzoyl-L-arginine-p-nitroanilide hydrochloride)
10 µl	protease inhibitor (10 µM or 75 µg/ml HF 7665 in H_2O)

The reaction was started by adding the chromogenic substrate, and the substrate conversion was followed by a photometer at λ = 405 nm. After about five minutes, 10 µl of protease inhibitor or the corresponding controls were added and the further course of the absorbance observed.

It could be shown that HF 7665 has an inhibitory effect on trypsin in a final concentration of about 1 µM or 7.5 µg/ml. Control experiments with corresponding amounts of BSA (7.5 µg/ml) and acetonitrile/TFA (0.8% ACN/0.001% TFA) did not show any trypsin inhibition. Further, an inhibitory effect of HF 7665 on chymotrypsin could not be observed in a similar test.

Figure 3 shows that the substrate conversion is reduced by about 30% due to trypsin inhibition after the addition of HF 7665.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Prof. Dr. Wolf-Georg Forssmann

(B) STREET: Feodor-Lynen-Str. 31

(C) CITY: Hannover

(E) COUNTRY: Germany

(F) POSTAL CODE: 30625

(ii) TITLE OF INVENTION: Serine Protease Inhibitors

(iii) NUMBER OF SEQUENCES: 34

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 177 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Met Lys Ile Ala Thr Val Ser Val Leu Leu Pro Leu Ala Leu Cys Leu
1               5                  10                  15
```

```
Ile Gln Asp Ala Ala Ser Lys Asn Glu Asp Gln Glu Met Cys His Glu
            20                  25                  30

Phe Gln Ala Phe Met Lys Asn Gly Lys Leu Phe Cys Pro Gln Asp Lys
        35                  40                  45

Lys Phe Phe Gln Ser Leu Asp Gly Ile Met Phe Ile Asn Lys Cys Ala
    50                  55                  60

Thr Cys Lys Met Ile Leu Glu Lys Glu Ala Lys Ser Gln Lys Arg Ala
65                  70                  75                  80

Arg His Leu Ala Arg Ala Pro Lys Ala Thr Ala Pro Thr Glu Leu Asn
                85                  90                  95

Cys Asp Asp Phe Lys Lys Gly Glu Arg Asp Gly Asp Phe Ile Cys Pro
            100                 105                 110

Asp Tyr Tyr Glu Ala Val Cys Gly Thr Asp Gly Lys Thr Tyr Asp Asn
        115                 120                 125

Arg Cys Ala Leu Cys Ala Glu Asn Ala Lys Thr Gly Ser Gln Ile Gly
    130                 135                 140

Val Lys Ser Glu Gly Glu Cys Lys Ser Ser Asn Pro Glu Gln Val Arg
145                 150                 155                 160

Ser Ile Val Ser Leu Met Gly Asn Thr Gly Arg Leu Thr Ser Asn Ser
                165                 170                 175

Lys
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 922 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
Met Lys Ile Ala Thr Val Ser Val Leu Leu Pro Leu Ala Leu Cys Leu
1               5                   10                  15

Ile Gln Asp Ala Ala Ser Lys Asn Glu Asp Gln Glu Met Cys His Glu
            20                  25                  30
```

```
Phe Gln Ala Phe Met Lys Asn Gly Lys Leu Phe Cys Pro Gln Asp Lys
        35                  40                  45

Lys Phe Phe Gln Ser Leu Asp Gly Ile Met Phe Ile Asn Lys Cys Ala
    50                  55                  60

Thr Cys Lys Met Ile Leu Glu Lys Glu Ala Lys Ser Gln Lys Arg Ala
65                  70                  75                  80

Arg His Leu Ala Arg Ala Pro Lys Ala Thr Ala Pro Thr Glu Leu Asn
                85                  90                  95

Cys Asp Asp Phe Lys Lys Gly Glu Arg Asp Gly Asp Phe Ile Cys Pro
            100                 105                 110

Asp Tyr Tyr Glu Ala Val Cys Gly Thr Asp Gly Lys Thr Tyr Asp Asn
        115                 120                 125

Arg Cys Ala Leu Cys Ala Glu Asn Ala Lys Thr Gly Ser Gln Ile Gly
    130                 135                 140

Val Lys Ser Glu Gly Glu Cys Lys Ser Ser Asn Pro Glu Gln Asp Val
145                 150                 155                 160

Cys Ser Ala Phe Arg Pro Phe Val Arg Asn Gly Arg Leu Gly Cys Thr
                165                 170                 175

Arg Glu Asn Asp Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly Asn
            180                 185                 190

Lys Cys Ala Met Cys Ala Glu Leu Phe Leu Lys Glu Ala Glu Asn Ala
        195                 200                 205

Lys Arg Glu Gly Glu Thr Arg Ile Arg Arg Asn Ala Glu Lys Asp Phe
    210                 215                 220

Cys Lys Glu Tyr Glu Lys Gln Val Arg Asn Gly Arg Leu Phe Cys Thr
225                 230                 235                 240

Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Arg Met His Gly Asn
                245                 250                 255

Lys Cys Ala Leu Cys Ala Glu Ile Phe Lys Arg Arg Phe Ser Glu Glu
            260                 265                 270

Asn Ser Lys Thr Asp Gln Asn Leu Gly Lys Ala Glu Glu Lys Thr Lys
        275                 280                 285

Val Lys Arg Glu Ile Val Lys Leu Cys Ser Gln Tyr Gln Asn Gln Ala
    290                 295                 300

Lys Asn Gly Ile Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Arg Gly
305                 310                 315                 320

Pro Asp Gly Lys Met His Gly Asn Leu Cys Ser Met Cys Gln Val Tyr
                325                 330                 335

Phe Gln Ala Glu Asn Glu Glu Lys Lys Lys Ala Glu Ala Arg Ala Arg
            340                 345                 350
```

```
Asn Lys Arg Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Asn
        355                 360                 365

Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu
    370                 375                 380

Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys
385                 390                 395                 400

Ser Met Cys Glu Val Phe Phe Gln Ala Glu Glu Glu Glu Lys Lys Lys
                405                 410                 415

Lys Glu Gly Glu Ser Arg Asn Lys Arg Gln Ser Lys Ser Thr Ala Ser
            420                 425                 430

Phe Glu Glu Leu Cys Ser Glu Tyr Arg Lys Ser Arg Lys Asn Gly Arg
        435                 440                 445

Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys
    450                 455                 460

Met His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln Gln Glu
465                 470                 475                 480

Glu Arg Ala Arg Ala Lys Ala Lys Arg Glu Ala Ala Lys Glu Ile Cys
                485                 490                 495

Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile Cys Thr Arg
            500                 505                 510

Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys
        515                 520                 525

Cys Ala Met Cys Ala Ser Val Phe Lys Leu Glu Glu Glu Glu Lys Lys
    530                 535                 540

Asn Asp Lys Glu Glu Lys Gly Lys Val Glu Ala Glu Lys Val Lys Arg
545                 550                 555                 560

Glu Ala Val Gln Glu Leu Cys Ser Glu Tyr Arg His Tyr Val Arg Asn
                565                 570                 575

Gly Arg Leu Pro Cys Thr Arg Glu Asn Asp Pro Ile Glu Gly Leu Asp
            580                 585                 590

Gly Lys Ile His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln
        595                 600                 605

Gln Glu Ala Lys Glu Lys Glu Arg Ala Glu Pro Arg Ala Lys Val Lys
    610                 615                 620

Arg Glu Ala Glu Lys Glu Thr Cys Asp Glu Phe Arg Arg Leu Leu Gln
625                 630                 635                 640

Asn Gly Lys Leu Phe Cys Thr Arg Glu Asn Asp Pro Val Arg Gly Pro
                645                 650                 655
```

```
Asp Gly Lys Thr His Gly Asn Lys Cys Ala Met Cys Lys Ala Val Phe
            660                 665                 670

Gln Lys Glu Asn Glu Glu Arg Lys Arg Lys Glu Glu Glu Asp Gln Arg
        675                 680                 685

Asn Ala Ala Gly His Gly Ser Ser Gly Gly Gly Gly Gly Asn Thr Gln
    690                 695                 700

Asp Glu Cys Ala Glu Tyr Arg Glu Gln Met Lys Asn Gly Arg Leu Ser
705                 710                 715                 720

Cys Thr Arg Glu Ser Asp Pro Val Arg Asp Ala Asp Gly Lys Ser Tyr
                725                 730                 735

Asn Asn Gln Cys Thr Met Cys Lys Ala Lys Leu Glu Arg Glu Ala Glu
            740                 745                 750

Arg Lys Asn Glu Tyr Ser Arg Ser Arg Ser Asn Gly Thr Gly Ser Glu
        755                 760                 765

Ser Gly Lys Asp Thr Cys Asp Glu Phe Arg Ser Gln Met Lys Asn Gly
    770                 775                 780

Lys Leu Ile Cys Thr Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly
785                 790                 795                 800

Lys Thr His Gly Asn Lys Cys Thr Met Cys Lys Glu Lys Leu Glu Arg
                805                 810                 815

Glu Ala Ala Glu Lys Lys Arg Lys Arg Met Lys Thr Gly Ala Ile Gln
            820                 825                 830

Glu Lys Gly Ala Ile Gln Glu Lys Gly Ala Met Thr Lys Arg Ile Cys
        835                 840                 845

Val Val Asn Phe Glu Ala Cys Arg Glu Met Glu Ser Leu Ser Ala Pro
    850                 855                 860

Glu Lys Ile Thr Leu Phe Glu Ala His Met Ala Arg Cys Thr Ser Ile
865                 870                 875                 880

Asn Val Leu Cys Val Arg Ala Ser Leu Ile Glu Lys Leu Met Lys Glu
                885                 890                 895

Lys Arg Lys Met Lys Arg Asn Gln Val Ala Ser Pro Gln Ile Met Gln
            900                 905                 910

Arg Met Ser Ala Val Asn Phe Glu Thr Ile
        915                 920
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 55 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
Lys Asn Glu Asp Gln Glu Met Cys His Glu Phe Gln Ala Phe Met Lys
1               5                  10                  15

Asn Gly Lys Leu Phe Cys Pro Gln Asp Lys Lys Phe Phe Gln Ser Leu
            20                  25                  30

Asp Gly Ile Met Phe Ile Asn Lys Cys Ala Thr Cys Lys Met Ile Leu
        35                  40                  45

Glu Lys Glu Ala Lys Ser Gln
    50                  55
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 68 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Asn Glu Tyr Arg
1               5                  10                  15

Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu Asn Asp Pro
            20                  25                  30

Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys Ser Met Cys
        35                  40                  45
```

Glu Val Phe Phe Gln Ala Glu Glu Glu Glu Lys Lys Lys Lys Glu Gly
50 55 60

Glu Ser Arg Asn
65

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 748 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

ATGCATGGAG TGGACCTGTA GGCGACTTGC ATCGTCTTCA ACATGAAGAT AGCCACAGTG 60

TCAGTGCTTC TGCCCTTGGC TCTTTGCCTC ATACAAGATG CTGCCAGTAA GAATGAAGAT 120

CAGGAAATGT GCCATGAATT TCAGGCATTT ATGAAAAATG GAAAACTGTT CTGTCCCCAG 180

GATAAGAAAT TTTTTCAAAG TCTTGATGGA ATAATGTTCA TCAATAAATG TGCCACGTGC 240

AAAATGATAC TGGAAAAAGA AGCAAAATCA CAGAAGAGGG CCAGGCATTT AGCAAGAGCT 300

CCCAAGGCTA CTGCCCCAAC AGAGCTGAAT TGTGATGATT TTAAAAAAGG AGAAAGAGAT 360

GGGGATTTTA TCTGTCCTGA TTATTATGAA GCTGTTTGTG GCACAGATGG GAAAACATAT 420

GACAACAGAT GTGCACTGTG TGCTGAGAAT GCGAAAACCG GGTCCCAAAT TGGTGTAAAA 480

AGTGAAGGGG AATGTAAGAG CAGTAATCCA GAGCAGGTGA GGTCAATTGT CAGCCTGATG 540

GGAAATACTG GGAGGCTAAC TTCAAATAGT AAGTAGGTGC TGTCCTCTTC CTTCTTAGGT 600

GGGAGCCTTG GAAGGAATTA ATTCTTGCTT TATGTGAAAT GGAATACCCA GTTACTGCCC 660

ACTAATATGA AAAAGCTAAT TATAGTCTCT GAAACTGGAT CAGATTACTT TGGTGGTTAA 720

GATCTTTCAA TCTATTGCTG CTTTGTAT 748

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3531 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```
ATGCATGGAG TGGACCTGTA GGCGACTTGC ATCGTCTTCA ACATGAAGAT AGCCACAGTG      60
TCAGTGCTTC TGCCCTTGGC TCTTTGCCTC ATACAAGATG CTGCCAGTAA GAATGAAGAT     120
CAGGAAATGT GCCATGAATT TCAGGCATTT ATGAAAAATG GAAAACTGTT CTGTCCCCAG     180
GATAAGAAAT TTTTTCAAAG TCTTGATGGA ATAATGTTCA TCAATAAATG TGCCACGTGC     240
AAAATGATAC TGGAAAAAGA AGCAAAATCA CAGAAGAGGG CCAGGCATTT AGCAAGAGCT     300
CCCAAGGCTA CTGCCCCAAC AGAGCTGAAT TGTGATGATT TTAAAAAAGG AGAAAGAGAT     360
GGGGATTTTA TCTGTCCTGA TTATTATGAA GCTGTTTGTG GCACAGATGG GAAAACATAT     420
GACAACAGAT GTGCACTGTG TGCTGAGAAT GCGAAAACCG GGTCCCAAAT TGGTGTAAAA     480
AGTGAAGGGG AATGTAAGAG CAGTAATCCA GAGCAGGATG TATGCAGTGC TTTTCGGCCC     540
TTTGTTAGAA ATGGAAGACT TGGATGCACA AGGGAAAATG ATCCTGTTCT TGGTCCTGAT     600
GGGAAGACGC ATGGCAATAA GTGTGCAATG TGTGCTGAGC TGTTTTTAAA AGAAGCTGAA     660
AATGCCAAGC GAGAGGGTGA AACTAGAATT CGACGAAATG CTGAAAAGGA TTTTTGCAAG     720
GAATATGAAA AACAAGTGAG AAATGGAAGG CTTTTTTGTA CACGGGAGAG TGATCCAGTC     780
CGTGGCCCTG ACGGCAGGAT GCATGGCAAC AAATGTGCCC TGTGTGCTGA AATTTTCAAG     840
CGGCGTTTTT CAGAGGAAAA CAGTAAAACA GATCAAAATT TGGGAAAAGC TGAAGAAAAA     900
ACTAAAGTTA AAAGAGAAAT TGTGAAACTC TGCAGTCAAT ATCAAAATCA GGCAAAGAAT     960
GGAATACTTT TCTGTACCAG AGAAAATGAC CCTATTCGTG GTCCAGATGG GAAAATGCAT    1020
GGCAACTTGT GTTCCATGTG TCAAGTCTAC TTCCAAGCAG AAAATGAAGA AAAGAAAAAG    1080
GCTGAAGCAC GAGCTAGAAA CAAAAGAGAA TCTGGAAAAG CAACCTCATA TGCAGAGCTT    1140
TGCAATGAAT ATCGAAAGCT TGTGAGGAAC GGAAAACTTG CTTGCACCAG AGAGAACGAT    1200
```

CCTATTCAGG GCCCAGATGG GAAAGTGCAC GGCAACACCT GCTCCATGTG TGAGGTTTTT 1260

TTCCAAGCAG AAGAAGAAGA AAAGAAAAAG AAGGAAGGCG AATCAAGAAA CAAAAGACAA 1320

TCTAAGAGTA CAGCTTCCTT TGAGGAGTTG TGTAGTGAAT ACCGCAAATC CAGGAAAAAC 1380

GGACGGCTTT TTTGCACCAG AGAGAATGAC CCCATCCAGG GCCCAGATGG GAAAATGCAT 1440

GGCAACACCT GCTCCATGTG TGAGGCCTTC TTTCAACAAG AAGAAAGAGC AAGAGCAAAG 1500

GCTAAAAGAG AAGCTGCAAA GGAAATCTGC AGTGAATTTC GGGACCAAGT GAGGAATGGA 1560

ACACTTATAT GCACCAGGGA GCATAATCCT GTCCGTGGAC CAGATGGCAA AATGCATGGA 1620

AACAAGTGTG CCATGTGTGC CAGTGTGTTC AAACTTGAAG AAGAAGAGAA GAAAAATGAT 1680

AAAGAAGAAA AAGGGAAAGT TGAGGCTGAA AAAGTTAAGA GAGAAGCAGT TCAGGAGCTG 1740

TGCAGTGAAT ATCGTCATTA TGTGAGGAAT GGACGACTCC CCTGTACCAG AGAGAATGAT 1800

CCTATTGAGG GTCTAGATGG GAAAATCCAC GGCAACACCT GCTCCATGTG TGAAGCCTTC 1860

TTCCAGCAAG AAGCAAAAGA AAAAGAAAGA GCTGAACCCA GAGCAAAAGT CAAAAGAGAA 1920

GCTGAAAAGG AGACATGCGA TGAATTTCGG AGACTTTTGC AAAATGGAAA ACTTTTCTGC 1980

ACAAGAGAAA ATGATCCTGT GCGTGGCCCA GATGGCAAGA CCCATGGCAA CAAGTGTGCC 2040

ATGTGTAAGG CAGTCTTCCA GAAAGAAAAT GAGGAAAGAA AGAGGAAAGA AGAGGAAGAT 2100

CAGAGAAATG CTGCAGGACA TGGTTCCAGT GGTGGTGGAG GAGGAAACAC TCAGGACGAA 2160

TGTGCTGAGT ATCGGGAACA AATGAAAAAT GGAAGACTCA GCTGTACTCG GGAGAGTGAT 2220

CCTGTACGTG ATGCTGATGG CAAATCGTAC AACAATCAGT GTACCATGTG TAAAGCAAAA 2280

TTGGAAAGAG AAGCAGAGAG AAAAAATGAG TATTCTCGCT CCAGATCAAA TGGGACTGGA 2340

TCAGAATCAG GGAAGGATAC ATGTGATGAG TTTAGAAGCC AAATGAAAAA TGGAAAACTT 2400

ATCTGCACTC GAGAAAGTGA CCCTGTCCGG GGTCCAGATG GCAAGACACA TGGTAATAAG 2460

TGTACTATGT GTAAGGAAAA ACTGGAAAGG GAAGCAGCTG AAAAAAAAAG AAAGAGGATG 2520

AAGACAGGAG CAATACAGGA GAAAGGAGCA ATACAGGAGA AAGGAGCAAT GACAAAGAGG 2580

ATCTGTGTCG TGAATTTCGA AGCATGCAGA GAAATGGAAA GCTTATCTGC ACCAGAGAAA 2640

ATAACCCTGT TCGAGGCCCA TATGGCAAGA TGCACATCAA TAAATGTGCT ATGTGTCAGA 2700

GCATCTTTGA TCGAGAAGCT AATGAAAGAA AAAAGAAAGA TGAAGAGAAA TCAAGTAGCA 2760

AGCCCTCAAA TAATGCAAAG GATGAGTGCA GTGAATTTCG AAACTATATA AGGAACAATG 2820

AACTCATCTG CCCTAGAGAG AATGACCCAG TGCACGGTGC TGATGGAAAG TTCTATACAA 2880

ACAAGTGCTA CATGTGCAGA GCTGTCTTTC TAACAGAAGC TTTGGAAAGG GCAAAGCTTC 2940

AAGAAAAACC ATCCCATGTT AGAGCTTCTC AAGAGGAAGA CAGCCCAGAC TCTTTCAGTT 3000

CTCTGGATTC TGAGATGTGC AAAGACTACC GAGTATTGCC CAGGATAGGC TATCTTTGTC 3060

CAAAGGATTT AAAGCCTGTC TGTGGTGACG ATGGCCAAAC CTACAACAAT CCTTGCATGC 3120

TCTGTCATGA AAACCTGATA CGCCAAACAA ATACACACAT CCGCAGTACA GGGAAGTGTG 3180

AGGAGAGCAG CACCCCAGGA ACCACCGCAG CCAGCATGCC CCCGTTTGAC GAATGACAGG 3240

AAGATTGTTG AAAGCCATGA GGGAAAAAAT AAACCCCAGT TTTGAATCAC CTACCTTCAC 3300

CATCTGTATA TACAAAGAAT TTTTCGGAGC TTGTTTTATT TGCTATAGAA AACAATACAG 3360

AGCTTTTGGG AATGGAATCA CTGATTTTCA GTCTTTTCCA TTTCTTTCCT CCTAGAATCT 3420

GTGATCTGAG GGTATAAAGA CATTTCCACC AAGTTTGAGC CCTCAAAATG TCCTGATTAC 3480

AATGCTGTCT GTCCAACTGC CTGTTCAATA AAAGTAAACT CAGCAGAAAA A 3531

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
His Glu Phe Gln Ala Phe Met Lys Asn Gly Lys Leu Phe
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Ser Glu Tyr Arg Lys Ser Arg Lys Asn Gly Arg Leu Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Asp Asp Phe Lys Lys Gly Glu Arg Asp Gly Asp Phe Ile
1 5 10

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile
1 5 10

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Ser Ala Phe Arg Pro Phe Val Arg Asn Gly Arg Leu Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Ser Glu Tyr Arg His Tyr Val Arg Asn Gly Arg Leu Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Lys Glu Tyr Glu Lys Gln Val Arg Asn Gly Arg Leu Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
Asp Glu Phe Arg Arg Leu Leu Gln Asn Gly Lys Leu Phe
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

```
Ser Gln Tyr Gln Asn Gln Ala Lys Asn Gly Ile Leu Phe
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

```
Ala Glu Tyr Arg Glu Gln Met Lys Asn Gly Arg Leu Ser
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

```
Asn Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

```
Asp Glu Phe Arg Ser Gln Met Lys Asn Gly Lys Leu Ile
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

```
Pro Gln Asp Lys Lys Phe Phe Gln Ser Leu Asp Gly Ile Met Phe Ile
1               5                   10                  15

Asn Lys
```

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

```
Thr Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys Met His Gly
1               5                   10                  15

Asn Thr
```

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

```
Thr Arg Glu Asn Asp Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly
1               5                   10                  15

Asn Lys
```

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

```
Thr Arg Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly
1               5                   10                  15

Asn Lys
```

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

```
Thr Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Arg Met His Gly
1               5                  10                  15

Asn Lys
```

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

```
Thr Arg Glu Asn Asp Pro Ile Glu Gly Leu Asp Gly Lys Ile His Gly
1               5                  10                  15

Asn Thr
```

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

```
Thr Arg Glu Asn Asp Pro Ile Arg Gly Pro Asp Gly Lys Met His Gly
1               5                  10                  15

Asn Leu
```

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

```
Thr Arg Glu Asn Asp Pro Val Arg Gly Pro Asp Gly Lys Thr His Gly
1               5                   10                  15

Asn Lys
```

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

```
Thr Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly
1               5                   10                  15

Asn Thr
```

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

```
Thr Arg Glu Ser Asp Pro Val Arg Asp Ala Asp Gly Lys Ser Tyr Asn
1               5                  10                  15

Asn Gln
```

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

```
Thr Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Lys Thr His Gly
1               5                  10                  15

Asn Lys
```

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Ala Thr
1

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ala Leu
1

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Ala Met
1

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Ser Met
1

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Thr Met
1

CLAIMS:

1. A serine protease inhibitor, characterized by having a domain with four cysteines, and a sequence of 13 amino acids is present between the first and second cysteines, a sequence of 18 amino acids is present between the second and third cysteines, and a sequence of 2 amino acids is present between the third and fourth cysteines.

2. The serine protease inhibitor according to claim 1, characterized in that the sequence of the domain between the first and second cysteines is selected from

HEFQAFMKNGKLF,
DDFKKGERDGDFI,
SAFRPFVRNGRLG,
KEYEKQVRNGRLF,
SQYQNQAKNGILF,
NEYRKLVRNGKLA,
SEYRKSRKNGRLF,
SEFRDQVRNGTLI,
SEYRHYVRNGRLP,
DEFRRLLQNGKLF,
AEYREQMKNGRLS, or
DEFRSQMKNGKLI.

3. The serine protease inhibitor according to any of claims 1 and/or 2, characterized in that the sequence between the second and third cysteines is selected from

PQDKKFFQSLDGIMFINK,
TRENDPVLGPDGKTHGNK,
TRESDPVRGPDGRMHGNK,
TRENDPIRGPDGKMHGNL,
TRENDPIQGPDGKVHGNT,
TRESDPVRGPDGKTHGNK.
TRENDPIQGPDGKMHGNT,
TREHNPVRGPDGKMHGNK,
TRENDPIEGLDGKIHGNT,
TRENDPVRGPDGKTHGNK,
TRESDPVRDADGKSYNNQ, or

4. The serine protease inhibitor according to any of claims 1 to 3, characterized in that the sequence between the third and fourth cysteines of the domain is selected from

AT, AL, AM, SM, or TM.

5. The serine protease inhibitor according to any of claims 1 to 4, having one of the following formulas:

R_1-C-HEFQAFMKNGKLF-C-PQDKKFFQSLDGIMFINK-C-AT-C-R_2
R_1-C-DDFKKGERDGDFI-C-PDYYEAVCGTDGKTYDNR-C-AL-C-R_2
R_1-C-SAFRPFVRNGRLG-C-TRENDPVLGPDGKTHGNK-C-AM-C-R_2
R_1-C-KEYEKQVRNGRLF-C-TRESDPVRGPDGRMHGNK-C-AL-C-R_2
R_1-C-SQYQNQAKNGILF-C-TRENDPIRGPDGKMHGNL-C-SM-C-R_2
R_1-C-NEYRKLVRNGKLA-C-TRENDPIQGPDGKVHGNT-C-SM-C-R_2
R_1-C-SEYRKSRKNGRLF-C-TRENDPIQGPDGKMHGNT-C-SM-C-R_2
R_1-C-SEFRDQVRNGTLI-C-TREHNPVRGPDGKMHGNK-C-AM-C-R_2
R_1-C-SEYRHYVRNGRLP-C-TRENDPIEGLDGKIHGNT-C-SM-C-R_2
R_1-C-DEFRRLLQNGKLF-C-TRENDPVRGPDGKTHGNK-C-AM-C-R_2
R_1-C-AEYREQMKNGRLS-C-TRESDPVRDADGKSYNNQ-C-TM-C-R_2
R_1-C-DEFRSQMKNGKLI-C-TRESDPVRGPDGKTHGNK-C-TM-C-R_2,

wherein R_1 is NH_2, an amino acid, or a peptide with up to 1000 amino acids, and R_2 is COOH, $CONH_2$, an amino acid, or a peptide with up to 1000 amino acids.

6. The serine protease inhibitor according to at least one of claims 1 to 5, characterized by containing

- a disulfide bridge between the first and fourth cysteines and/or between the second and third cysteines; or

- a disulfide bridge between the first and fifth cysteines and/or between the second and fourth cysteines and/or between the third and sixth cysteines.

7. The serine protease inhibitor according to at least one of claims 1 to 6, characterized by being a fragment of VAKTI-1 (SEQ. ID. NO. 1) or VAKTI-2 (SEQ. ID. NO. 2).

8. The serine protease inhibitor according to claim 7, characterized by being HF 6479 (SEQ. ID. NO. 3) or HF 7665 (SEQ. ID. NO. 4).

9. A nucleic acid coding for a serine protease inhibitor according to at least one of claims 1 to 8.

10. A medicament containing at least one serine protease inhibitor according to at least one of claims 1 to 8 and/or a nucleic acid according to claim 9, optionally together with pharmaceutical vehicles.

11. The medicament according to claim 10, containing from 0.01 to 1000 mg per kg of body weight of the serine protease inhibitor according to at least one of claims 1 to 8 and/or of the nucleic acid according to claim 9.

12. Use of the serine protease inhibitor according to at least one of claims 1 to 8 for preparing a medicament for the treatment of acute or chronic cervix inflammations, inflammations of Bartholin's glands and other vaginal regions, tonsillitis, pharyngitis and laryngitis, acute or chronic inflammatory processes accompanied by excessive formation of mucus and the resulting acute emergency situations, postoperative bleedings due to hyperfibrinolysis, and for the prophylaxis of lung emphysema formation in deficiencies of α_1-proteinase inhibitor.

13. Use of the nucleic acids according to claim 9 for preparing a medicament for use in gene therapy for the curing and prophylaxis of diseases as mentioned in claim 12.

14. Antibodies or antibody fragments against epitopes of the compounds according to any of claims 1 to 8.

15. Poly- or oligonucleotides which will hybridize to regions of the cDNA or corresponding RNA under stringent conditions and optionally prevent the expression of coding regions of the genes coding for the compounds according to claims 1 to 8 (antisense compounds).

16. A diagnostic agent containing at least one of the compounds according to claim 14 or 15.

17. A medicament containing at least one of the compounds mentioned in claims 14 and/or 15 in therapeutically effective amounts.

18. Use of the compounds according to claims 14 and/or 15 for preparing a medicament for the treatment of diseases involving too high an expression of the compounds according to at least one of claims 1 to 8, or too high an activity of the regions coding for the compounds according to claims 1 to 8.

19. DNA, coding for the compounds mentioned in claims 1 to 8, and/or RNA involved in the transcription or translation of the compounds mentioned in claims 1 to 8.

20. The DNA according to claim 19 having the SEQ. ID. NO. 5 or SEQ. ID. NO. 6.

Abstract

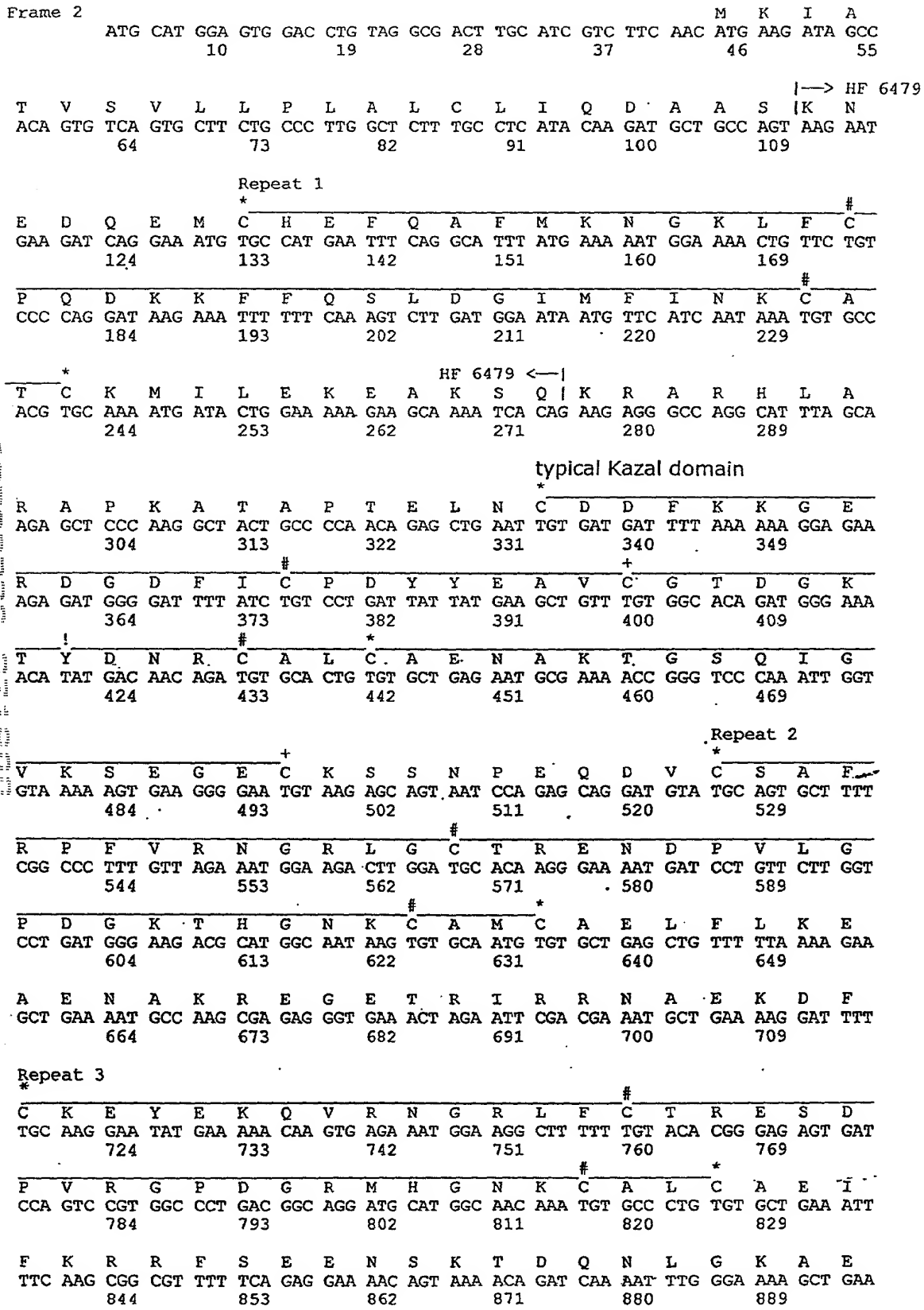
A serine protease inhibitor, characterized by having a domain with four cysteines, and a sequence of 0 to 20 amino acids is present between the first and second cysteines, or the serine protease inhibitor has a domain with six cysteines, and a sequence of 7 to 20 amino acids is present between the first and second cysteines.

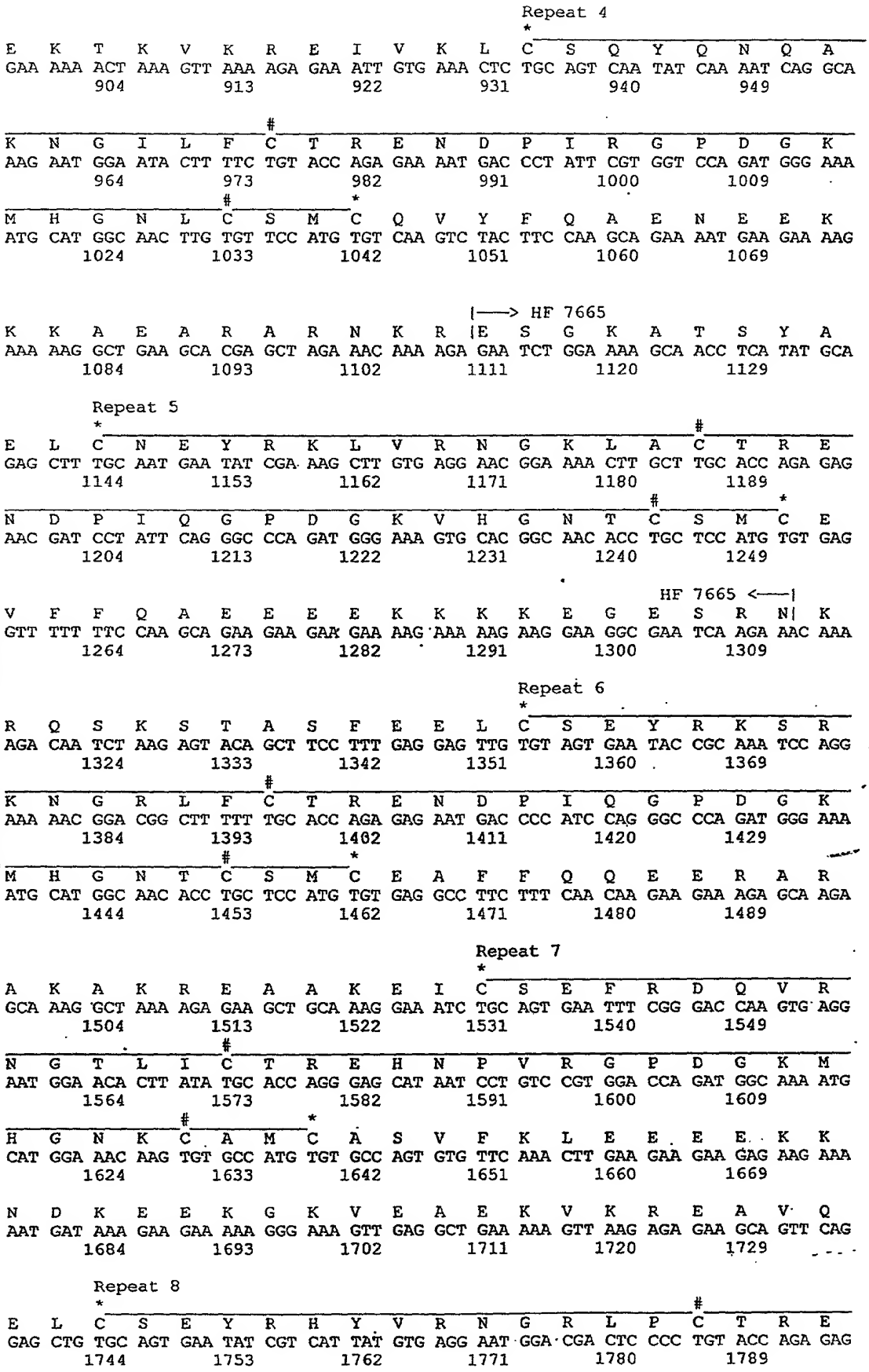
Figure 1
VAKTI-1 cDNA and its translation into amino acid sequence

```
Frame 2                                                                 M   K   I   A
          ATG CAT GGA GTG GAC CTG TAG GCG ACT TGC ATC GTC TTC AAC ATG AAG ATA GCC
                    10          19          28          37          46          55

                                                                        |---MEMC-1->
                                                                        |->HF6479
T   V   S   V   L   L   P   L   A   L   C   L   I   Q   D   A   A   S  |K   N
ACA GTG TCA GTG CTT CTG CCC TTG GCT CTT TGC CTC ATA CAA GAT GCT GCC AGT AAG AAT
          64          73          82          91          100         109

----------MEMC-1---------> <-----------------CHEF-1------------------->
E   D   Q   E   M   C   H   E   F   Q   A   F   M   K   N   G   K   L   F   C
GAA GAT CAG GAA ATG TGC CAT GAA TTT CAG GCA TTT ATG AAA AAT GGA AAA CTG TTC TGT
          124         133         142         151         160         169

     <-------------------CHEF-14-----------------
     ---------------------CHEF-11--------------------->                <----CHEF-2---
P   Q   D   K   K   F   F   Q   S   L   D   G   I   M   F   I   N   K   C   A
CCC CAG GAT AAG AAA TTT TTT CAA AGT CTT GAT GGA ATA ATG TTC ATC AAT AAA TGT GCC
          184         193         202         211         220         229

<----------CHEF-2----------                  HF6479 <----|
T   C   K   M   I   L   E   K   E   A   K   S   Q  |K   R   A   R   H   L   A
ACG TGC AAA ATG ATA CTG GAA AAA GAA GCA AAA TCA CAG AAG AGG GCC AGG CAT TTA GCA
          244         253         262         271         280         289

R   A   P   K   A   T   A   P   T   E   L   N   C   D   D   F   K   K   G   E
AGA GCT CCC AAG GCT ACT GCC CCA ACA GAG CTG AAT TGT GAT GAT TTT AAA AAA GGA GAA
          304         313         322         331         340         349

R   D   G   D   F   I   C   P   D   Y   Y   E   A   V   C   G   T   D   G   K
AGA GAT GGG GAT TTT ATC TGT CCT GAT TAT TAT GAA GCT GTT TGT GGC ACA GAT GGG AAA
          364         373         382         391         400         409

T   Y   D   N   R   C   A   L   C   A   E   N   A   K   T   G   S   Q   I   G
ACA TAT GAC AAC AGA TGT GCA CTG TGT GCT GAG AAT GCG AAA ACC GGG TCC CAA ATT GGT
          424         433         442         451         460         469

V   K   S   E   G   E   C   K   S   S   N   P   E   Q   V   R   S   I   V   S
GTA AAA AGT GAA GGG GAA TGT AAG AGC AGT AAT CCA GAG CAG GTG AGG TCA ATT GTC AGC
          484         493         502         511         520         529

L   M   G   N   T   G   R   L   T   S   N   S   K   STOP
CTG ATG GGA AAT ACT GGG AGG CTA ACT TCA AAT AGT AAG TAG GTG CTG TCC TCT TCC TTC
          544         553         562         571         580         589

TTA GGT GGG AGC CTT GGA AGG AAT TAA TTC TTG CTT TAT GTG AAA TGG AAT ACC CAG TTA
          604         613         622         631         640         649

CTG CCC ACT AAT ATG AAA AAG CTA ATT ATA GTC TCT GAA ACT GGA TCA GAT TAC TTT GGT
          664         673         682         691         700         709

GGT TAA GAT CTT TCA ATC TAT TGC TGC TTT GTA T
          724         733         742       749
```

Figure 2

VAKTI-2 cDNA and its translation into amino acid sequence

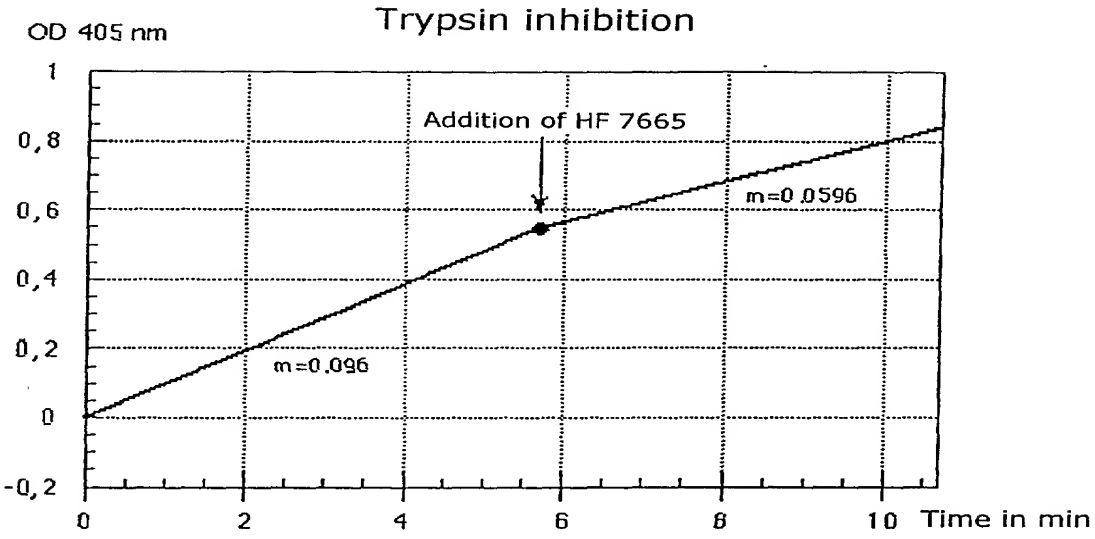



Repeat 4
E K T K V K R E I V K L C S Q Y Q N Q A
GAA AAA ACT AAA GTT AAA AGA GAA ATT GTG AAA CTC TGC AGT CAA TAT CAA AAT CAG GCA
904 913 922 931 940 949
K N G I L F C T R E N D P I R G P D G K
AAG AAT GGA ATA CTT TTC TGT ACC AGA GAA AAT GAC CCT ATT CGT GGT CCA GAT GGG AAA
964 973 982 991 1000 1009
M H G N L C S M C Q V Y F Q A E N E E K
ATG CAT GGC AAC TTG TGT TCC ATG TGT CAA GTC TAC TTC CAA GCA GAA AAT GAA GAA AAG
1024 1033 1042 1051 1060 1069
HF 7665
K K A E A R A R N K R E S G K A T S Y A
AAA AAG GCT GAA GCA CGA GCT AGA AAC AAA AGA GAA TCT GGA AAA GCA ACC TCA TAT GCA
1084 1093 1102 1111 1120 1129
Repeat 5
E L C N E Y R K L V R N G K L A C T R E
GAG CTT TGC AAT GAA TAT CGA AAG CTT GTG AGG AAC GGA AAA CTT GCT TGC ACC AGA GAG
1144 1153 1162 1171 1180 1189
N D P I Q G P D G K V H G N T C S M C E
AAC GAT CCT ATT CAG GGC CCA GAT GGG AAA GTG CAC GGC AAC ACC TGC TCC ATG TGT GAG
1204 1213 1222 1231 1240 1249
HF 7665
V F F Q A E E E E K K K K E G E S R N K
GTT TTT TTC CAA GCA GAA GAA GAA GAA AAG AAA AAG AAG GAA GGC GAA TCA AGA AAC AAA
1264 1273 1282 1291 1300 1309
Repeat 6
R Q S K S T A S F E E L C S E Y R K S R
AGA CAA TCT AAG AGT ACA GCT TCC TTT GAG GAG TTG TGT AGT GAA TAC CGC AAA TCC AGG
1324 1333 1342 1351 1360 1369
K N G R L F C T R E N D P I Q G P D G K
AAA AAC GGA CGG CTT TTT TGC ACC AGA GAG AAT GAC CCC ATC CAG GGC CCA GAT GGG AAA
1384 1393 1402 1411 1420 1429
M H G N T C S M C E A F F Q Q E E R A R
ATG CAT GGC AAC ACC TGC TCC ATG TGT GAG GCC TTC TTT CAA CAA GAA GAA AGA GCA AGA
1444 1453 1462 1471 1480 1489
Repeat 7
A K A K R E A A K E I C S E F R D Q V R
GCA AAG GCT AAA AGA GAA GCT GCA AAG GAA ATC TGC AGT GAA TTT CGG GAC CAA GTG AGG
1504 1513 1522 1531 1540 1549
N G T L I C T R E H N P V R G P D G K M
AAT GGA ACA CTT ATA TGC ACC AGG GAG CAT AAT CCT GTC CGT GGA CCA GAT GGC AAA ATG
1564 1573 1582 1591 1600 1609
H G N K C A M C A S V F K L E E E E K K
CAT GGA AAC AAG TGT GCC ATG TGT GCC AGT GTG TTC AAA CTT GAA GAA GAA GAG AAG AAA
1624 1633 1642 1651 1660 1669
N D K E E K G K V E A E K V K R E A V Q
AAT GAT AAA GAA GAA AAA GGG AAA GTT GAG GCT GAA AAA GTT AAG AGA GAA GCA GTT CAG
1684 1693 1702 1711 1720 1729
Repeat 8
E L C S E Y R H Y V R N G R L P C T R E
GAG CTG TGC AGT GAA TAT CGT CAT TAT GTG AGG AAT GGA CGA CTC CCC TGT ACC AGA GAG
1744 1753 1762 1771 1780 1789

```
                                                                  #         *
N   D   P   I   E   G   L   D   G   K   I   H   G   N   T   C   S   M   C   E
AAT GAT CCT ATT GAG GGT CTA GAT GGG AAA ATC CAC GGC AAC ACC TGC TCC ATG TGT GAA
        1804        1813        1822        1831        1840        1849

A   F   F   Q   Q   E   A   K   E   K   E   R   A   E   P   R   A   K   V   K
GCC TTC TTC CAG CAA GAA GCA AAA GAA AAA GAA AGA GCT GAA CCC AGA GCA AAA GTC AAA
        1864        1873        1882        1891        1900        1909

                                Repeat 9
                                *
R   E   A   E   K   E   T   C   D   E   F   R   R   L   L   Q   N   G   K   L
AGA GAA GCT GAA AAG GAG ACA TGC GAT GAA TTT CGG AGA CTT TTG CAA AAT GGA AAA CTT
        1924        1933        1942        1951        1960        1969

    #
F   C   T   R   E   N   D   P   V   R   G   P   D   G   K   T   H   G   N   K
TTC TGC ACA AGA GAA AAT GAT CCT GTG CGT GGC CCA GAT GGC AAG ACC CAT GGC AAC AAG
        1984        1993        2002        2011        2020        2029

#
C   A   M   C   K   A   V   F   Q   K   E   N   E   E   R   K   R   K   E   E
TGT GCC ATG TGT AAG GCA GTC TTC CAG AAA GAA AAT GAG GAA AGA AAG AGG AAA GAA GAG
        2044        2053        2062        2071        2080        2089

E   D   Q   R   N   A   A   G   H   G   S   S   G   G   G   G   G   N   T   Q
GAA GAT CAG AGA AAT GCT GCA GGA CAT GGT TCC AGT GGT GGT GGA GGA GGA AAC ACT CAG
        2104        2113        2122        2131        2140        2149

Repeat 10
        *                                                       #
D   E   C   A   E   Y   R   E   Q   M   K   N   G   R   L   S   C   T   R   E
GAC GAA TGT GCT GAG TAT CGG GAA CAA ATG AAA AAT GGA AGA CTC AGC TGT ACT CGG GAG
        2164        2173        2182        2191        2200        2209

                                                              #         *
S   D   P   V   R   D   A   D   G   K   S   Y   N   N   Q   C   T   M   C   K
AGT GAT CCT GTA CGT GAT GCT GAT GGC AAA TCG TAC AAC AAT CAG TGT ACC ATG TGT AAA
        2224        2233        2242        2251        2260        2269

A   K   L   E   R   E   A   E   R   K   N   E   Y   S   R   S   R   S   N   G
GCA AAA TTG GAA AGA GAA GCA GAG AGA AAA AAT GAG TAT TCT CGC TCC AGA TCA AAT GGG
        2284        2293        2302        2311        2320        2329

                                    Repeat 11
                                    *
T   G   S   E   S   G   K   D   T   C   D   E   F   R   S   Q   M   K   N   G
ACT GGA TCA GAA TCA GGG AAG GAT ACA TGT GAT GAG TTT AGA AGC CAA ATG AAA AAT GGA
        2344        2353        2362        2371        2380        2389

        #
K   L   I   C   T   R   E   S   D   P   V   R   G   P   D   G   K   T   H   G
AAA CTT ATC TGC ACT CGA GAA AGT GAC CCT GTC CGG GGT CCA GAT GGC AAG ACA CAT GGT
        2404        2413        2422        2431        2440        2449

        #           *
N   K   C   T   M   C   K   E   K   L   E   R   E   A   A   E   K   K   R   K
AAT AAG TGT ACT ATG TGT AAG GAA AAA CTG GAA AGG GAA GCA GCT GAA AAA AAA AGA AAG
        2464        2473        2482        2491        2500        2509

R   M   K   T   G   A   I   Q   E   K   G   A   I   Q   E   K   G   A   M   T
AGG ATG AAG ACA GGA GCA ATA CAG GAG AAA GGA GCA ATA CAG GAG AAA GGA GCA ATG ACA
        2524        2533        2542        2551        2560        2569

K   R   I   C   V   V   N   F   E   A   C   R   E   M   E   S   L   S   A   P
AAG AGG ATC TGT GTC GTG AAT TTC GAA GCA TGC AGA GAA ATG GAA AGC TTA TCT GCA CCA
        2584        2593        2602        2611        2620        2629
```

```
E   K   I   T   L   F   E   A   H   M   A   R   C   T   S   I   N   V   L   C
GAG AAA ATA ACC CTG TTC GAG GCC CAT ATG GCA AGA TGC ACA TCA ATA AAT GTG CTA TGT
       2644        2653        2662        2671        2680        2689

V   R   A   S   L   I   E   K   L   M   K   E   K   R   K   M   K   R   N   Q
GTC AGA GCA TCT TTG ATC GAG AAG CTA ATG AAA GAA AAA AGA AAG ATG AAG AGA AAT CAA
       2704        2713        2722        2731        2740        2749

V   A   S   P   Q   I   M   Q   R   M   S   A   V   N   F   E   T   I   STOP
GTA GCA AGC CCT CAA ATA ATG CAA AGG ATG AGT GCA GTG AAT TTC GAA ACT ATA TAA GGA
       2764        2773        2782        2791        2800        2809

ACA ATG AAC TCA TCT GCC CTA GAG AGA ATG ACC CAG TGC ACG GTG CTG ATG GAA AGT TCT
       2824        2833        2842        2851        2860        2869

ATA CAA ACA AGT GCT ACA TGT GCA GAG CTG TCT TTC TAA CAG AAG CTT TGG AAA GGG CAA
       2884        2893        2902        2911        2920        2929

AGC TTC AAG AAA AAC CAT CCC ATG TTA GAG CTT CTC AAG AGG AAG ACA GCC CAG ACT CTT
       2944        2953        2962        2971        2980        2989

TCA GTT CTC TGG ATT CTG AGA TGT GCA AAG ACT ACC GAG TAT TGC CCA GGA TAG GCT ATC
       3004        3013        3022        3031        3040        3049

TTT GTC CAA AGG ATT TAA AGC CTG TCT GTG GTG ACG ATG GCC AAA CCT ACA ACA ATC CTT
       3064        3073        3082        3091        3100        3109

GCA TGC TCT GTC ATG AAA ACC TGA TAC GCC AAA CAA ATA CAC ACA TCC GCA GTA CAG GGA
       3124        3133        3142        3151        3160        3169

AGT GTG AGG AGA GCA GCA CCC CAG GAA CCA CCG CAG CCA GCA TGC CCC CGT TTG ACG AAT
       3184        3193        3202        3211        3220        3229

GAC AGG AAG ATT GTT GAA AGC CAT GAG GGA AAA AAT AAA CCC CAG TTT TGA ATC ACC TAC
       3244        3253        3262        3271        3280        3289

CTT CAC CAT CTG TAT ATA CAA AGA ATT TTT CGG AGC TTG TTT TAT TTG CTA TAG AAA ACA
       3304        3313        3322        3331        3340        3349

ATA CAG AGC TTT TGG GAA TGG AAT CAC TGA TTT TCA GTC TTT TCC ATT TCT TTC CTC CTA
       3364        3373        3382        3391        3400        3409

GAA TCT GTG ATC TGA GGG TAT AAA GAC ATT TCC ACC AAG TTT GAG CCC TCA AAA TGT CCT
       3424        3433        3442        3451        3460        3469

                                  polyadenylation signal
GAT TAC AAT GCT GTC TGT CCA ACT GCC TGT TCA ATA AAA GTA AAC TCA GCA GAA AAA....
       3484        3493        3502        3511        3520        3529

.......poly(A) tail
```

Figure 3



DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT; PARIS CONVENTION, NON PRIORITY; OR PROVISIONAL APPLICATIONS

FOR ATTORNEYS' USE ONLY
ATTORNEYS' DOCKET NO. 2000

101 / 102

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

Serine Proteinase Inhibitors

which is described and claimed in:

[X] PCT International Application No PCT/EP 98/08424 filed 23 December 1998

[ ] the attached specification

[ ] the specification in application Serial No. _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

103

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
197 57 572.2	Germany	23 December 1997	[X]	[ ]
198 00 363.3	Germany	08 January 1998	[X]	[ ]
			[ ]	[ ]

104

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No _____ Filing Date _____

105

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

(Application Serial No.)	(Filing Date)	(Status patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); ALLEN S. MELSER (27,215); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

SEND CORRESPONDENCE TO: CUSTOMER NO. 00136 or	DIRECT TELEPHONE CALLS TO: (please use Attorney's Docket No.) (202) 638-6666
JACOBSON, PRICE, HOLMAN & STERN PROFESSIONAL LIMITED LIABILITY COMPANY 400 SEVENTH STREET, N.W. WASHINGTON, D.C. 20004	JACOBSON, PRICE, HOLMAN & STERN PROFESSIONAL LIMITED LIABILITY COMPANY

*Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME * OF INVENTOR	FAMILY NAME: FORSSMANN	GIVEN NAME: Wolf-Georg	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Hannover	STATE OR FOREIGN COUNTRY: Germany DEX	COUNTRY OF CITIZENSHIP: German	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: Feodor-Lynen-Strasse 31	CITY: Hannover	STATE OR COUNTRY: Germany	ZIP CODE: D-30625
202	FULL NAME * OF INVENTOR	FAMILY NAME: MAGERT	GIVEN NAME: Hans-Jürgen	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Hannover	STATE OR FOREIGN COUNTRY: Germany DEX	COUNTRY OF CITIZENSHIP: German	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: Moltkeplatz 8	CITY: Hannover	STATE OR COUNTRY: Germany	ZIP CODE: D-30163
203	FULL NAME * OF INVENTOR	FAMILY NAME: STÄNDKER	GIVEN NAME: Ludger	MIDDLE NAME:	
	RESIDENCE & CITIZENSHIP	CITY: Hannover	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: German DEX	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: Dohmeyers Weg 25	CITY: Hannover	STATE OR COUNTRY: Germany	ZIP CODE: D-30625

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE 06/15/00	DATE 06/15/00	DATE 06/15/00

[X] Additional inventors are named on separately numbered sheets attached hereto.

JACOBSON, PRICE, HOLMAN & STERN
ADDITIONAL INVENTORS

* Inventor(s) name must include at least one unabbreviated first or middle name

204	FULL NAME * OF INVENTOR	FAMILY NAME KREUZTMANN	GIVEN NAME Peter	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY Magdeburg	STATE OR FOREIGN COUNTRY Germany	COUNTRY OF CITIZENSHIP German	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS Rautenbreite 11	CITY Magdeburg	STATE OR COUNTRY Germany	ZIP CODE D-39116
205	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
206	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
207	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
208	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
209	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
210	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
211	FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 204* P. Kreutzmann	SIGNATURE OF INVENTOR 205*	SIGNATURE OF INVENTOR 206*
DATE 06/15/00	DATE	DATE
SIGNATURE OF INVENTOR 207*	SIGNATURE OF INVENTOR 208*	SIGNATURE OF INVENTOR 209*
DATE	DATE	DATE
SIGNATURE OF INVENTOR 210*	SIGNATURE OF INVENTOR 211*	
DATE	DATE	

☐ Additional inventors are named on separately numbered sheets attached hereto